REMARKS

Status Summary

Claims 15-20 are pending. Claims 1-14 were canceled previously. Claims 15-20 were examined on the merits considering a species selected by the applicant. This species was free of the prior art. The examiner then selected additional species for examination on the basis that none of the claims are directed uniquely to the selected species. The additional species were also found to be free of the prior art. Claims 15-20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. Claims 15-16 are also rejected under 35 U.S.C. § 112, first paragraph, as allegedly indefinite. Claim 15 is rejected under 35 U.S.C. 102 (b) as allegedly anticipated by U.S. Patent No. 5,442,043 to Fukuta et al. Reconsideration in view of the following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph, - Written Description

Claims 15-20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. The examiner states that the specification fails to provide a representative number of species to support the genus of A-B thiol-containing conjugates, as set forth in claims 15-20. In particular, the examiner states that there is insufficient description in the specification to support the individual elements, which are combined to form the claimed conjugates. The examiner contends that somatostatin peptides, fragments thereof, variants thereof and the thiol-binding therapeutic agents are not adequately supported. Official action, pages 5-6. In addition, the examiner states that the possible structural variations of the claimed genus of A-B thiol-containing conjugates lack sufficient support because there is no restriction regarding how A binds B and/or the many possible somatostatin analog and prodrugs that may be used to make the generic structure. Official action, pages 6-7. The examiner also asserts that the full breadth of the biological activity of the claimed conjugates encompassed by the claims is insufficiently supported. Official action, page 6.

In order to comply with the written description requirement, "[t]he applicant must . . . convey to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). The

descriptive text needed to meet these requirements "varies with the nature and scope of the invention at issue, and with the scientific knowledge already in existence." *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005).

In *Capon*, both parties to a patent interference appealed the decision of the Board of Patent Appeals and Interferences ("the Board") that the claims of either party failed to meet the written description requirement of 35 U.S.C. § 112, first paragraph. The claims at issue were directed to chimeric genes designed to enhance immune responses using known DNA sequences of known function. The Court of Appeals for the Federal Circuit held that the Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula of possible DNA components of the chimeric genes. The court explained that the Capon and Eshhar inventions did not concern discovering which DNA segments were related to the immune response, which was in the prior art, but in the novel combination of the DNA segments to achieve a novel result. The court also stated that the Board's requirement that the sequences of the component DNA be reported in the specification does not add descriptive substance. A person experienced in the field of the invention would understand that the known DNA segments retain their DNA sequences when linked by known methods. *See Capon*, 418 F.3d at 1349, 76 USPQ2d at 1085.

With respect to claim scope, the court in *Capon* further disagreed with the Board's conclusion that it can not be known whether all of the permutations and combinations covered by the claims will be effective for the intended purpose. The court stated that compliance with the written description requirement does not require that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. The court found that the claims of both parties were supported by general teachings of how to select and recombine the DNA and by specific examples of the production of chimeric genes. In addition, the court stated that the Board's observation that the full scope of the claims appears enabled cannot be reconciled with the Board's rationale that only a general plan to combine unidentified DNA is disclosed. *See Capon*, at 1086.

Similar to the facts in *Capon*, the instant claims encompass a novel combination of known elements with known function to achieve a novel result. The instant specification teaches

the skilled artisan how to select and combine the known elements, *i.e.*, somatostatin peptides, fragments or variants thereof, and therapeutic agents, to derive the claimed conjugates that can be used to treat SSTR-associated disorders. Based upon the general teachings of how to combine these known elements and the specific examples provided in the originally filed application, the instant disclosure is sufficient to allow a skilled artisan to envision the genus of the A-B thiol-containing conjugates that are used in the methods as claimed.

Somatostatin peptides are well-known in the art and are described in the specification on page 6, lines 11-21. Somatostatin peptides are peptides capable of binding to a somatostatin receptor (page 16, lines 11-12). Examples of such somatostatin peptides are included in the sequence listing (SEQ ID NOS. 4 and 8) and described in 16 patents referenced in the specification on page 6, lines 18-21, and specifically incorporated into the instant specification by reference. Somatostatin peptides that are capable of binding to somatostatin receptors are well-characterized in the prior art. Thus, a skilled artisan understands amino acid residues and/or secondary or tertiary structures necessary for somatostatin peptides to bind to somatostatin receptors. In addition, a skilled artisan is able to readily determine the binding ability of any particular somatostatin variant to a somatostatin receptor. Accordingly, the present application adequately describes the somatostatin peptides, fragments, and variants that are encompassed by the instant claims.

Therapeutic agents of the conjugates useful in the claimed methods are also adequately described. Therapeutic agents that may be used to make the instantly claimed compound combinations are disclosed, for example, on pages 17-20 in the specification as filed. These agents include radioisotopes, cytotoxins, immunostimulatory agents, anti-angiogenic agents, therapeutic genes and chemotherapeutic agents, which are further exemplified in the specification as filed. (*See e.g.*, specific isotopes on page 18, lines 18-29; cytotoxins on page 18, lines 12-13; immunostimulatory agents on page 19, lines 14-20; anti-angiogenic agents on page 19, lines 21-31, to page 20, line 2). The instant specification also discloses that therapeutic agents, which are capable of forming a thiol linkage, are suitable for use in the present invention (*see e.g.*, page 4, lines 10-12). Thus, a skilled artisan can readily envision the genus of therapeutic agents that may be conjugated to the somatostatin analogs of the present invention.

In addition, the specification adequately describes how the A and B peptide chains may be combined to form somatostatin analogs and further combined with therapeutic agents to derive the instantly claimed conjugates. For example, the somatostatin analogs are designed so as to provide site-specific drug attachment via a thiol linkage. The site for drug attachment is selected as an interior site removed from residues involved in ligand binding. (*see* page 7, lines 30-33, and page 8, lines 1-7). The thiol linkages are further described in the specification on pages 11-12 and include direct linkages, indirect linkages, such as with chelators, and stable or labile linkages. Thus, the specification provides a thorough description of the elements that may be used to derive the claimed A-B peptide thiol-containing conjugates as well as how these elements are combined.

In further support of the scope of the claims, the specification provides examples demonstrating the structures and biological activities of two species of somatostatin analog/therapeutic agent conjugates. Examples 4 and 5 describe the cytotoxic and anti-tumor effect of CP1-AEB and CP1-FKMMAE, respectively. As stated in *Capon*, the specification does not need to describe every permutation of a claimed combination to comply with the written description requirement. In the instant case, because the invention involves a novel combination of known elements having known biological activities (*i.e.*, an ability of an A-B analog to bind a somatostatin receptor and an ability of a therapeutic agent to have a biological activity when delivered to a cell), the knowledge in the art is extensive. In addition, the level of skill in the art with respect to peptide engineering and peptide conjugation is high. Thus, based upon the specific examples provided in the specification, which are supported by the general teachings and knowledge in the art, as described above, a skilled artisan would understand the co-inventors to be in possession of the full scope of conjugates useful for performing the claimed methods.

In summary, similar to the facts in *Capon*, the instant specification teaches a skilled artisan how to select and combine components having known structure and function to derive the conjugates useful in the claimed methods. The specification further provides specific examples that demonstrate the structures and biological activities of the disclosed conjugates for their intended purpose, *i.e.*, treating SSTR-associated disorders. Thus, the instant specification provides a skilled artisan with sufficient disclosure to allow him to readily envision the structure and properties of the conjugates for practice of the claimed methods. For the reasons set forth

above, applicants submit that the present specification complies with 35 U.S.C. § 112, first paragraph. Applicants respectfully request that the rejection of claims 15-20 be withdrawn.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 15-16 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, the examiner states that the phrase "wherein A is a single cysteine residue," as used in claim 16, is allegedly vague because claim 15 specifies that A "is a peptide chain." Claim 15 is amended to specify that A is a peptide chain *or* a single amino acid comprising one or more cysteine residues. Support for the claim is found throughout the specification and in original claim 16. Based thereon, applicants respectfully request the rejection be withdrawn.

Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 15-20 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,442,043 to Fukuta et al. ("Fukuta"). The examiner alleges that a species of the carrier peptide conjugate of Fukuta, *i.e.*, the insulin-somatostatin conjugate described in Figure 6 and Example 10 of Fukata, teaches all of the elements of the instant claims. Specifically, the examiner contends that the insulin chain F007 of the Fukuta patent may be considered equivalent to the A peptide, as specified in the instant claims, and that somatostatin as described in the Fukata patent may be considered equivalent to the B peptide, as in the instant claims. In addition, the examiner states that Figure 6 of the Fukuta patent shows that thiol linkages are between the insulin A and B chains and that each one of the chains can be deemed a therapeutic agent. Official action, pages 8-10. In assessing the elements of the instant claims and the disclosure of the Fukata patent, the examiner alleges that the preamble and "wherein clause" of claim 15, which specifies that the claimed somatostatin analogs are bound to a therapeutic agent via a thiol linkage to the one or more cysteine residues of (A) at an interior site, is not deemed to be limiting because the clause does not modify the claims structurally. (Official action, page 10).

An anticipating reference must fully disclose each and every element of the claimed invention, arranged as in the claim. *See Lindemnn Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452 (Fed. Cir. 1984). A claim preamble is considered an element of the

claim if, when read in the context of the entire claim, it is 'necessary to give life, meaning, and vitality' to the claim. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999). In considering the effect of the preamble in a claim directed to a method of treatment, language specifying a subject "in need thereof" gives life and meaning to the claim. *See Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003). The determination of whether or not a wherein clause is a limitation in a claim depends on the specific facts of the case. *Hoffer v. Microsoft Corp.*, 405 F.3d 1326 74 USPQ2d 1481 (Fed. Cir. 2005). When the clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention. *Hoffer*, at 1483.

In response to the rejection of claims under 35 U.S.C. § 102(b), applicants submit that the Fukata patent does not anticipate the presently pending claims for lack of disclosure of all of the elements of the claim. As described further below, the preamble and wherein clause of originally filed claim 15 specify elements of the claim, *i.e.*, that the claimed method includes administration of a composition as disclosed, that such composition comprises a therapeutic agent bound to the somatostatin analog (A-B), and that administration of the composition results in treatment of a SSTR-associated disorder.

The present claims are directed to a method for treating an SSTR-associated disorder in a mammalian subject by administering to the subject a composition, which includes a component for binding SSTR and a component which is a therapeutic agent. Initially, applicants disagree with the examiner's characterization of claim 15 as not requiring elements set forth in the preamble and in wherein or whereby clauses. Specifically, the preamble of the claim specifies that a composition is administered for treating an SSTR-related disorder. In addition, the therapeutic agent in the "wherein clause" specifies that the therapeutic agent is bound to the claimed somatostatin analogs via a thiol linkage to the cysteines in the A region of the somatostatin analog, which is a structural element of the administered conjugate. To clarify that such elements are indeed patentable elements of the claim, the preamble of claim 15 is amended to specify that the conjugate is administered to a subject in need thereof as described in the originally filed specification on page 17, line 32, through page 18, line 4. In addition, the term "composition" is replaced with "conjugate" to more clearly state the physical relationship

between the somatostatin analog and therapeutic agent, as described in original claim 15 and throughout the specification. Claim 15 is further amended to place elements of the wherein clause more clearly in the body of the claim. Accordingly, the examiner's comments with respect to limitations that do not constitute patentable elements of the claim are rendered moot.

As amended, claim 15 sets forth at least the following five (5) elements: (a) administering a conjugate for treatment of a SSTR-related disorder to a subject in need thereof; (b) said conjugate comprising a somatostatin analog and a therapeutic agent; (c) said somatostatin analog having a formula (A-B); wherein A is a peptide or a single amino acid comprising one or more cysteine residues, and wherein B is a naturally occurring or synthetic peptide or fragment thereof which binds to a somatostatin receptor; (d) said somatostatin analog and therapeutic agent being bound via a thiol linkage; and (e) said administration of the composition elicits effects for treatment of a SSTR-related disorder.

In response to the rejection of claims as allegedly anticipated by Fukata, applicants submit that the Fukata patent fails to teach each of the above-noted five patentable elements of claim 15. The Fukuta patent describes a peptide conjugate capable of passing the blood-brain barrier comprising (1) a bioactive peptide or protein incapable of passing the blood-brain barrier (*e.g.*, somatostatin), and (2) a carrier peptide which exhibits substantially no bioactivity and which is capable of passing the blood-brain barrier, which is a conjugate of fragments of the amino-terminal regions of insulin (*i.e.*, fragments of insulin peptide A and insulin peptide B, which are joined by thiol linkages as depicted in Figure 6 of Fukata). Conjugation of the elements of (1) and (2) makes it possible to allow a bioactive peptide or protein incapable of passing the blood-brain barrier to easily pass the blood-brain for uniform transport to the brain without any side effect of the carrier peptide.

The examiner alleges that the bioactive peptide (1) of Fukata is analogous to subpart B of the somatostatin analog (A-B) of the present claims, and that carrier peptide (2) of Fukata is analogous to subpart A of the somatostatin analog (A-B) of the present claims to thereby arrive at the instant invention. Applicants disagree with the examiner's analysis based upon the following. The conjugates of Fukata lack a therapeutic agent, which is bound to a somatostatin analog via a thiol linkage, as in claim 15. In addition, Fukata fails to describe treatment of an SSTR-related disorder by administration of a conjugate to a subject in need thereof.

With respect to the alleged structural analogy of the conjugates of Fukata and the instant invention, applicants note that the conjugate of Fukata does not include a therapeutic agent bound via a thiol linkage to a somatostatin peptide. The examiner points out that the fragments of insulin peptides A and B are joined via thiol linkages, and that either insulin peptide fragment may be considered a therapeutic agent. Applicants believe that the examiner's comparison is misguided on at least three grounds. First, Fukata makes clear that the fragments of insulin peptides A and B together form a "a carrier peptide which exhibits essentially no biological activity." Rather, fragments of insulin peptides A and B are selected based upon their ability to bind to cerebellar capillary endothelial cells, to traverse the blood-brain barrier, and to be without side effects. *See e.g.*, column 3, lines 12-35, of the Fukata patent. Accordingly, the insulin peptide fragments of Figure 6 of Fukata are not fairly considered therapeutic agents. Second, Fukata describes thiol linkages between the fragments of insulin peptides A and B, which form a carrier peptide conjugate. While the insulin peptide fragments are joined via thiol linkages to form the carrier peptide, as noted by the examiner, Fukata does not describe linkage of a somatostatin analog and a therapeutic agent via a thiol linkage, as presently claimed. Third, the somatostatin analog (A-B) of the present claims is a peptide, which in turn is conjugated to a therapeutic agent. Following the examiner's analogy, the somatostatin/insulin analog of Fukata is comparable to the somatostatin analog (A-B), which lacks a third component of a therapeutic agent.

In addition to the above-noted distinctions, Fukata does not describe administering a conjugate for treatment of a SSTR-related disorder to a subject in need thereof. As described in the instant application, an SSTR-related disorder is a condition characterized by abnormal SSTR expression and/or function. *See* page 7, lines 3-16, of the originally filed application. To achieve treatment of an SSTR-related disorder, the instant invention discloses a method for targeting of a therapeutic agent to SSTR-expressing cells by conjugation of a somatostatin analog and a therapeutic agent. Specifically, the somatostatin analog serves as the targeting component of the conjugate.

In contrast to the present invention, the conjugates of Fukata are targeted to brain cells such as cerebellar capillary endothelial cells, which are bound by the carrier peptide comprising fragments of insulin peptides A and B. Fukata describes somatostatin-containing conjugates,

wherein somatostatin functions not as a targeting molecule, as in the instant application, but rather as a therapeutic agent. *See e.g.*, column 3, line 58, through column 4, line 26, of Fukata. It is unclear from the disclosure of Fukata as to whether the therapeutic activities of somatostatin are useful for treatment of SSTR-related disorders characterized by abnormal somatostatin expression or function, as in claim 15. Thus, Fukata does not describe administering conjugates for treatment of a SSTR-related disorder to a subject in need thereof, as presently claimed.

Based upon the foregoing, the Fukuta patent does not anticipate claim 15 in that it fails to describe the at least patentable five (5) patentable elements (a)-(e) as described herein above. Accordingly, applicants respectfully request that the rejection of claim 15 under 35 U.S.C. § 102(b) be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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